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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,714	FLEGEL ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *13 and 15-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7, 9-12, 14, 48, and 50-51* is/are rejected.

7)☒ Claim(s) *6,8 and 49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-51 are pending.

2. Claims 13, and 15-47 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 1-12, 14, and 48-51 are being acted upon in this Office Action.

4. In view of the amendment filed 5/21/04, the following objection and rejections remain.

5. The disclosure stands objected to because of the following informality: the arrangement of the specification. See Arrangement of the Specification in Action mailed 9/25/01. Appropriate correction is required. The request that the objection be held in abeyance until such time allowable subject is indicated is acknowledged.

6. The drawings, filed 10/4/00, stand not approved. The request that the objection be held in abeyance until such time allowable subject is indicated is acknowledged.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-5, 7, 9-12, 14, 48, and 50-51 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) an isolated nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one missense mutation in its transmembrane and/or intracellular regions as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41 wherein the missense mutation occurs in nucleotide position 8 from C to G, nucleotide position 29 from G to A, nucleotide position 48 from G to C, nucleotide position 340 from C to T, nucleotide position 446 from C to A, nucleotide position 544 from T to A, nucleotide position 594 from A to T, nucleotide position 602 from C to G, nucleotide position 658 from T to C, nucleotide position

667 from T to G, nucleotide position 809 from T to G, nucleotide position 819 from G to A, nucleotide position 826 from G to C, nucleotide position 830 from G to A, nucleotide position 845 from G to A, nucleotide position 880 from G to C, nucleotide position 885 from G to T, nucleotide position 919 from G to A, nucleotide position 1016 from G to A, nucleotide position 1154 from G to C and nucleotide position 1177 from T to C of SEQ ID NO: 41 or a combination thereof, (2) An isolated nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one missense mutation in SEQ ID NO: 41 wherein the missense mutation results in amino acid substitution in the Rhesus D antigen at position selected from the group consisting of 3 from Ser to Cys, 10 from Arg to Gln, 16 from Trp to Cys, 114 from Arg to Trp, 149 from Ala to Asp, 182 from Ser to Thr, 198 from Lys to Asn, 201 from Thr to Arg, 220 from Trp to Arg, 223 from Phe to Val, 270 from Val to Gly, 276 from Ala to Pro, 277 from Gly to Glu, 282 from Gly to Asp, 294 from Ala to Pro, 295 from Met to Ile, 307 from Gly to Arg, 339 from Gly to Glu, 385 from Gly to Ala and 383 from Trp to Arg with the proviso that said D antigen does not carry not carry a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or of threonine in position 283 by isoleucine, (3) a vector comprising the nucleic acid molecule mentioned above, (4) a host cell transformed with said vector, (5) a method of producing a Rhesus D antigen contributing to the weak D phenotype comprising culturing said host cell under suitable conditions and isolating the Rhesus D antigen produced for diagnosis and screening assays, and (6) an oligonucleotide selected from the group consisting of SEQ ID NOS: 3-4, 7, 16-18, 20, 23, 25-26, 29-30 and 39-40 that hybridize under 0.1X SSC, 0.1% SDS at 65°C hybridization and washing conditions to a portion of SEQ ID NO: 41 comprising said at least one missense mutations or to the complementary portion thereof or hybridizing to a region involving the breakpoint of the gene conversion identified in claim 2 for screening missense mutation in *RHD* gene, **does not** reasonably provide enablement for (1) *all* nucleic acid molecule encoding any human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one of *any* missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in its transmembrane and/or intracellular regions, (2) *all* nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule (a) carrying at least one any missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in amino acid positions such as the ones recited in claims 2-3, and 7 or carrying *any* gene conversion

involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene as set forth in claim 2, or carrying any and all missense mutation occurs in nucleotide position such as the ones recited in claim 5, (3) the nucleic acid molecules mentioned above wherein said molecule is any mRNA, or any genomic DNA, (4) A vector comprising any nucleic acid molecule mentioned above, (5) any host cell transformed with said vector, (6) A method of producing any Rhesus D antigen contributing to the weak D phenotype comprising culturing said host cell under suitable conditions and isolating the Rhesus D antigen produced, and (7) *any* oligonucleotide, *any* oliglonucleotide 12 to 50 or *any* oligonucleotide 15 to 24 nucleotides in length hybridizing under 0.1X SSC, 0.01%SSC, 0.1% SDS at 65°C hybridization and washing conditions to any portion of the nucleic acid mentioned above for any purpose. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The scope of the claimed nucleic acid molecule encoding a human Rhesus D antigen that contributed to or indicative the weak D phenotype encompasses all nucleic acid molecule carrying any missense mutation in its transmembrane and/or intracellular regions as compared to the wild type set forth as SEQ ID NO: 41.

The specification discloses only one polynucleotide of SEQ ID NO: 41 that encodes a wild type human Rhesus D antigen. The specification further discloses one or more missense mutations in SEQ ID NO: 41 that contribute to weak D phenotype wherein the missense mutations occurs in nucleotide position 8 is from C to G, position 29 from G to A, position 48 from G to C, position 340 from C to T, position 446 from C to A, position 544 from T to A, position 594 from A to T, position 602 from C to G, in position 658 from T to C, position 667 from T to G, position 809 from T to G, position from 819 from G to A, position 826 from G to C, position 830 from G to A, position 845 from G to A, position 880 from G to C, position 885 from

G to T, position 919 from G to A, position 1016 from G to A, position 1154 from G to C, and position 1177 from T to C of SEQ ID NO: 41 or in a combination of said position. An isolated nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one missense mutation in SEQ ID NO: 41 wherein the missense mutation results in amino acid substitution in the Rhesus D antigen at position selected from the group consisting of 3 from Ser to Cys, 10 from Arg to Gln, 16 from Trp to Cys, 114 from Arg to Trp, 149 from Ala to Asp, 182 from Ser to Thr, 198 from Lys to Asn, 201 from Thr to Arg, 220 from Trp to Arg, 223 from Phe to Val, 270 from Val to Gly, 276 from Ala to Pro, 277 from Gly to Glu, 282 from Gly to Asp, 294 from Ala to Pro, 295 from Met to Ile, 307 from Gly to Arg, 339 from Gly to Glu, 385 from Gly to Ala and 383 from Trp to Arg with the proviso that said D antigen does not carry not carry a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or of threonine in position 283 by isoleucine, (3) a vector comprising the nucleic acid molecule mentioned above, (4) a host cell transformed with said vector, (5) a method of producing a Rhesus D antigen contributing to the weak D phenotype comprising culturing said host cell under suitable conditions and isolating the Rhesus D antigen produced for diagnosis and screening assays, and (6) an oligonucleotide selected from the group consisting of SEQ ID NOS: 3-4, 7, 16-18, 20, 23, 25-26, 29-30 and 39-40 that hybridize under 0.1X SSC, 0.1% SDS at 65°C hybridization and washing conditions to a portion of SEQ ID NO: 41 comprising said at least one missense mutations or to the complementary portion thereof or hybridizing to a region involving the breakpoint of the gene conversion identified in claim 2 for screening missense mutation in *RHD* gene.

With the exception of the specific nucleic acid molecule encoding the specific missense mutations in the human Rhesus D antigen mentioned above that resulted in weak D phenotype, there is insufficient guidance and working example as to which base change or substitution (claim 1) in which codon in the nucleic acid molecule such as mRNA and genomic DNA that causes insertion of a different amino acid (missense mutation) in the transmembrane and/or intracellular regions of the human Rhesus D antigen encoded by SEQ ID No 41 that would result in a weak D phenotype. There is also insufficient guidance and working example as to which codons and the corresponding amino acids in the stated amino acid position such as 2-16, 114-149, 179-225, or/and 267 to 397 change to which amino acids, and the corresponding codon that would result in weak D phenotype. Likewise, the same reasoning applies to claims 3, 5, and 7. Not only the nucleic acid molecule encoding all human weak Rheusus D antigen have not been disclosed,

there is insufficient guidance as to which undisclosed nucleic acid molecule is mRNA or genomic DNA, including DNA from nature.

As to gene conversion involving exons 6 to 9, the specification discloses only one polynucleotide of SEQ ID NO: 41 that encodes the wild type human Rhesus D antigen. There is insufficient guidance as to the nucleic acid molecule that corresponds to exons 6 to 9 of human Rhesus D antigen and exons 6 to 9 of the "RHCE gene", much less which base change, and the corresponding amino acid substitution in the undisclosed nucleic acid molecule for any purpose. Even if the missense mutation is limited to the specific amino acid position such as the ones recited in claim 3 or the specific amino acid substitution such as the ones recited in claim 4, it is not clear if those positions and/or amino acid substitution are applicable to gene conversion involving exons 6 to 9 when replaced by the corresponding exons of the RHCE gene. Further, there is insufficient guidance as to which undisclosed amino acid to be substituted at the stated positions such as the ones recited in claims 3 and 7 or the stated nucleotide position in claim 5.

Given the lack of guidance as to the structure (i.e. nucleic acid sequence) having the specific missense mutations in the nucleic acid molecule encoding all weak human Rhesus D antigen, it follows that the vector and host cell comprising the undisclosed nucleic acid molecule are not enabled. It also follows that the method of producing all undisclosed weak Rhesus D antigen is not enabled.

Further, there is insufficient guidance and working example as to which undisclosed nucleotide within the full length mRNA and genomic DNA to be substitute, the corresponding amino acids to be substitute, much less about the combination of nucleotides and/or amino acid positions and whether the resulting nucleic acid molecule would result in weak D phenotype, in turn, would be useful for any purpose.

Stryer *et al*, of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al,* of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Skolnick *et al,* of record, teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire

document, Abstract in particular). Given the indefinite number of missense mutation in the nucleic acid molecule, it is unpredictable which undisclosed "nucleic acid molecule" contributes to weak D phenotype and would be useful for screening the presence of one or more missense mutation in Rh D antigens of blood of donor and recipient. Since the nucleic acid molecule is not enable, it follows that the vector and host cell comprising said undisclosed nucleic acid molecule is not enable. It also follows that any oligonucleotide hybridizing to any undisclosed nucleic acid molecule carrying any missense mutation is not enabled.

In addition to the problem of not having a structure (without the nucleotide sequence) as discussed above, the oligonucleotide in claim 14 must hybridize to a portion of the undisclosed nucleic acid molecule comprising at least one (more than one) missense mutations, let alone the complementary portion thereof. Even if the structure of the nucleic acid molecule carrying the specified missense mutations in its transmembrane and/or intracellular regions is recited in claim 1 or 2, the oligonucleotide without the nucleotide sequence has no structure. It is unpredictable which random sequence such as any oligonucleotide that is 12 to 50 or 15 to 24 nucleotides in length would hybridize specifically to the nucleotide encoding a human Rhesus D antigen with which missense mutations in its transmembrane and/or intracellular regions or the breakpoint region of the gene conversion that contribute to the weak D phenotype, in turn, would be useful for screening and diagnosis.

The state of the prior art as exemplified by Wallace *et al* (of record) and Sambrook *et al* (of record) is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Even if the probe is a 20mer, the total number of hits in a database search was 143,797,728, which suggest that some of the probes encompassed by the claims would not preferentially hybridize to a "nucleic acid molecule" that encodes a Rhesus D antigen. Since the undisclosed oligonucleotide would not hybridize specifically to the undisclosed nucleic acid molecule that encodes a Rhesus D antigen contributing to or indicative of the weak D phenotype, it follows that the oligonucleotide would not specifically hybridize to the "complementary portion thereof" or any region involving the breakpoint of the gene conversion as recited in claim 14. Since the oligonucleotide in claim 14 is not enabled, it follows that any kit comprising said oligonucleotide is not enable. Although the specific amino acids to be substituted are recited in the claim 4, the amino acid substitution in reference to which amino acid sequence is not recited in the claim.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

Applicants' arguments filed 5/21/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 1 and 2 cannot be said to encompass any missense mutation since claim 1 recites a nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D, said nucleic acid molecule carrying at least one missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO:41, in its transmembrane and/or intracellular regions while claim 2 recites a nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule a) comprising at least one missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO:41, in amino acid positions 2-16, 1 14-149, 179-225 or/and 267 to 397 with the proviso that said D antigen does carry not a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or of threonine in position 183 by isoleucine; or b) carrying a gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene. (2) An oligonucleotide hybridizing under 0.1X SSC, 0.1% SDS at 65°C hybridization and washing conditions to a portion of the nucleic acid molecule of any one of claims 1 or 2 comprising said at least one missense mutation or to the complementary portion thereof or hybridizing to a region involving the breakpoint of the gene conversion identified in claim 2.

In response to applicant's argument that claims 1 and 2 cannot be said to encompass any missense mutation, the scope of the claimed nucleic acid molecule encoding a human Rhesus D antigen that contributed to or indicative the weak D phenotype encompasses all nucleic acid molecule, including nucleic acid molecule found in nature, carrying any missense mutation in its transmembrane and/or intracellular regions as compared to the wild type set forth as SEQ ID NO: 41. It is noted that the nucleic acid as set forth in SEQ ID NO: 41 encodes the wild type human Rhesus D antigen. There is insufficient guidance as to the structure without the nucleotide sequence of all nucleic acid molecules carrying at least one or more missense mutations in the transmembrane and/or intracellular regions wherein the undisclosed nucleic acid molecule still encodes a human Rhesus D antigen that contributed to or indicative of the weak D phenotype. Further, there is also insufficient guidance and working example as to which codons and the

corresponding amino acids in the stated amino acid position such as 2-16, 114-149, 179-225, or/and 267 to 397 change to which amino acids, and the corresponding codon that would result in weak D phenotype. Likewise, the same reasoning applies to claims 3, 5, and 7. Not only the structure of the nucleic acid molecule encoding all human weak Rheusus D antigen have not been disclosed, there is insufficient guidance as to which undisclosed nucleic acid molecule is mRNA or genomic DNA, much less about which codon and corresponding amino acids to be substitute for which undisclosed amino acids, in turn, the resulting undisclosed nucleic acid molecule is still a weak D phenotype.

In addition to the problem of not having a structure (without the nucleotide sequence) as discussed above, the oligonucleotide in claim 14 must hybridize to a portion of the undisclosed nucleic acid molecule comprising at least one (more than one) missense mutations, let alone the complementary portion thereof. Even if the structure of the nucleic acid molecule carrying the specified missense mutations in its transmembrane and/or intracellular regions is recited in claim 1 or 2, the oligonucleotide in claim 14 encompasses any random sequence such as any oligonucleotide that is 12 to 50 or 15 to 24 nucleotides in length. Without guidance as to the structure of the oligonucleotides, it is unpredictable which undisclosed oligonucleotide would hybridize specifically to said nucleic acid molecule carrying the specified missense mutations in its transmembrane and/or intracellular regions or the breakpoint region of the gene conversion, in turn, would be useful for screening and diagnosis.

The state of the prior art as exemplified by Wallace *et al* (of record) and Sambrook *et al* (of record) is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Even if the probe is a 20mer, the total number of hits in a database search was 143,797,728, which suggest that some of the probes encompassed by the claims would not preferentially hybridize to a "nucleic acid molecule" that encodes a Rhesus D antigen. As to gene conversion involving exons 6 to 9, the specification discloses only one polynucleotide of SEQ ID NO: 41 that encodes the wild type human Rhesus D antigen. There is insufficient guidance as to the nucleic acid molecule that corresponds to exons 6 to 9 of human Rhesus D antigen and exons 6 to 9 of the "RHCE gene". A gene includes introns, exons and promoter. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art on how to use the broadly claimed species. For the above reasons, undue experimentation would be required to practice the claimed invention.

In response to applicant's argument that it is not necessary that the claimed nucleic acid molecules maintain the structure or function of a protein encoded by SEQ ID NO: 1, it is the Examiner's position that without the structure of the nucleic acid molecule encoding a human Rhesus D antigen carrying the specific missense mutation at the specified position that contributes to or indicative of the weak D phenotype, one of skill in the art would not know where to look, much less using the undisclosed nucleic acid molecule to screen for the weak D phenotype. Until the location and the specific amino acid substitution encoded by the claimed nucleic acid molecules are taught, the claims as written merely extend an invitation for one skilled in the art to further experimentation to arrive at the claimed invention.

9. Claims 1-5, 7, 9-12, 14, 48, and 50-51 stand are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *all* nucleic acid molecule encoding any human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one of *any* missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in its transmembrane and/or intracellular regions, (2) *all* nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule (a) carrying at least one any missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in amino acid positions such as the ones recited in claims 2-3, 7 or carrying *any* gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene as set forth in claim 2, or carrying any and all missense mutation occurs in nucleotide position such as the ones recited in claim 5, (3) the nucleic acid molecules mentioned above wherein said molecule is any mRNA, or any genomic DNA, (4) A vector comprising any nucleic acid molecule mentioned above, (5) any host cell transformed with said vector, (6) A method of producing any Rhesus D antigen contributing to the weak D phenotype comprising culturing said host cell under suitable conditions and isolating the Rhesus D antigen produced, and (7) *any* oligonucleotide, *any* oligonucleotide 12 to 50 or *any* oligonucleotide 15 to 24 nucleotides in length hybridizing under 0.1X SSC, 0.01%SSC, 0.1% SDS at 65°C hybridization and washing conditions to any portion of the nucleic acid mentioned above. The scope of the claimed nucleic

acid molecule encoding a human Rhesus D antigen that contributed to or indicative the weak D phenotype encompasses all nucleic acid molecule carrying any missense mutation in its transmembrane and/or intracellular regions as compared to the wild type set forth as SEQ ID NO: 41.

The specification discloses only one polynucleotide of SEQ ID NO: 41 that encodes a wild type human Rhesus D antigen. The specification further discloses one or more missense mutations in SEQ ID NO: 41 that contribute to weak D phenotype wherein the missense mutations occurs in nucleotide position 8 is from C to G, position 29 from G to A, position 48 from G to C, position 340 from C to T, position 446 from C to A, position 544 from T to A, position 594 from A to T, position 602 from C to G, in position 658 from T to C, position 667 from T to G, position 809 from T to G, position from 819 from G to A, position 826 from G to C, position 830 from G to A, position 845 from G to A, position 880 from G to C, position 885 from G to T, position 919 from G to A, position 1016 from G to A, position 1154 from G to C, and position 1177 from T to C of SEQ ID NO: 41 or in a combination of said position. An isolated nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one missense mutation in SEQ ID NO: 41 wherein the missense mutation results in amino acid substitution in the Rhesus D antigen at position selected from the group consisting of 3 from Ser to Cys, 10 from Arg to Gln, 16 from Trp to Cys, 114 from Arg to Trp, 149 from Ala to Asp, 182 from Ser to Thr, 198 from Lys to Asn, 201 from Thr to Arg, 220 from Trp to Arg, 223 from Phe to Val, 270 from Val to Gly, 276 from Ala to Pro, 277 from Gly to Glu, 282 from Gly to Asp, 294 from Ala to Pro, 295 from Met to Ile, 307 from Gly to Arg, 339 from Gly to Glu, 385 from Gly to Ala and 383 from Trp to Arg with the proviso that said D antigen does not carry not carry a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or of threonine in position 283 by isoleucine, (3) a vector comprising the nucleic acid molecule mentioned above, (4) a host cell transformed with said vector, (5) a method of producing a Rhesus D antigen contributing to the weak D phenotype comprising culturing said host cell under suitable conditions and isolating the Rhesus D antigen produced for diagnosis and screening assays, and (6) an oligonucleotide selected from the group consisting of SEQ ID NOS: 3-4, 7, 16-18, 20, 23, 25-26, 29-30 and 39-40 that hybridize under 0.1X SSC, 0.1% SDS at 65°C hybridization and washing conditions to a portion of SEQ ID NO: 41 comprising said at least one missense mutations or to the

complementary portion thereof or hybridizing to a region involving the breakpoint of the gene conversion identified in claim 2 for screening missense mutation in *RHD* gene.

Other than the nucleic acid molecule encoding the specific missense mutations mentioned above, there is inadequate written description about the structure associated with function of all nucleic acid molecule encoding a human Rhesus D antigen carrying at least one missense mutation as compared to the wild type that contributed to or indicative the weak D phenotype without the nucleotide sequence (claims 1-3, 5, 7, and 9), and the corresponding amino acid sequence (claim 4). Given the indefinite number of missense mutation, there is inadequate written description about which codon in the nucleic acid molecule such as mRNA and genomic DNA that causes insertion of a different amino acid (missense mutation) in the transmembrane and/or intracellular regions of the human Rhesus D antigen encoded by SEQ ID No 41 that would result in a weak D phenotype. The amino acids to be substitute at the stated amino acid position such as 2-16, 114-149, 179-225, or/and 267 to 397, and/or the corresponding codon within SEQ ID NO: 41 are not adequately described. Likewise, the same reasoning applies to claims 3, 5, and 7. Not only the nucleic acid sequence of the nucleic acid molecule encoding all human weak Rheusus D antigen such as the ones recited in claims 1-3, 5, 7, and 9 have not been described, there is insufficient written description about which undisclosed nucleic acid molecule is mRNA or genomic DNA found in nature.

As to gene conversion involving exons 6 to 9, the specification discloses only one polynucleotide of SEQ ID NO: 41 that encodes the wild type human Rhesus D antigen. The specification has not described the nucleic acid molecule that corresponds to exons 6 to 9 of human Rhesus D antigen and exons 6 to 9 of the "RHCE gene", much less about which base exchange would resulted in weak D phenotype.

Given the lack of a written description about the structure (i.e. nucleic acid sequence) of the nucleic acid molecule encoding all weak human Rhesus D antigen, it follows that all protein encoded by all undisclosed nucleic acid molecule having various amino acids substitution are not adequately described. It also follows that the vector and host cell comprising the undisclosed nucleic acid molecule and the method of producing all undisclosed weak Rhesus D antigen are not adequately described.

In addition to the problem of not having a structure (without the nucleotide sequence) as discussed above, the oligonucleotide in claim 14 must hybridize to a portion of the undisclosed nucleic acid molecule comprising at least one (more than one) missense mutations, let alone the

complementary portion thereof. There is insufficient written description about the oligonucleotide without the nucleotide sequence. Even if the structure of the nucleic acid molecule carrying the specified missense mutations in its transmembrane and/or intracellular regions is recited in claim 1 or 2, the oligonucleotide in claim 14 encompasses any random sequence such as any oligonucleotide that is 12 to 50 or 15 to 24 nucleotides in length. Without the structure of the oligonucleotides, the oligonucleotide in claim 14 is not adequately described. Since the oligonucleotide is not adequately describe, it follows that any kit comprising said "oligonucleotide" is not sufficient described. Given that the "nucleic acid molecule" is not adequately described, the complementary thereof and any region involving the breakpoint of the gene conversion are not adequately described for the same reasons mentioned above. It is noted that though the claimed invention is directed to "nucleic acid molecule", the principle still holds for the amino acid encoded by said "nucleic acid molecule". Sine only one polynucleotide of SEQ ID NO: 41 that encodes a wild type human Rhesus D antigen is disclosed and the specific nucleotide substitutions in SEQ ID NO: 41 are disclosed, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of nucleic acid molecule carrying all missense mutation to describe the genus. Given the indefinite number of oligonucleotide that may encompassed by the claim, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 5/21/04 have been fully considered but are not found persuasive.

Applicants' position is that the specification exemplifies 11 different nucleic acid molecules that encode a human Rhesus D antigen contributing to or indicative of a weak D phenotype. In particular, the different nucleic acid molecules encoding RHD genes have missense mutations at positions 8, 29, 48, 340, 446, 544, 594, 602, 658, 667, 809, 819, 826, 830, 845, 880, 885, 919, 1016, 1154 and 1177. In addition, an RHD gene conversion in which exons

6 to 9 have been replaced with the corresponding exons of RHCE that contributes to or is indicative of the weak D phenotype is also disclosed.

In response, none of the claims recite the specific 11 nucleic acid molecules encode a human Rhesus D antigen contributing to or indicative of a weak D phenotype. The scope of the claimed nucleic acid molecule encoding a human Rhesus D antigen that contributed to or indicative the weak D phenotype encompasses all nucleic acid molecule carrying any missense mutation in its transmembrane and/or intracellular regions as compared to the wild type set forth as SEQ ID NO: 41 to read on the nucleic acid found in nature. There are 10 exons encoding the human Rhesus D antigen (See Avent et al) with 13 transmembrane regions and 2 cytoplasmic domains (See Fig. 5 in Rouillac et al). There are 4 types of nucleotide for genomic or cDNA (A, T, C, G) at positions 8, 29, 48, 340, 446, 544, 594, 602, 658, 667, 809, 819, 826, 830, 845, 880, 885, 919, 1016, 1154 and 1177, and 5 type of base for mRNA (A, T, C, G, U) at positions 8, 29, 48, 340, 446, 544, 594, 602, 658, 667, 809, 819, 826, 830, 845, 880, 885, 919, 1016, 1154 and 1177. Applicant has identified only 21 missense mutations at positions 8, 29, 48, 340, 446, 544, 594, 602, 658, 667, 809, 819, 826, 830, 845, 880, 885, 919, 1016, 1154 and 1177. There are 20 naturally occurring amino acids at the corresponding nucleotide position. The claims encompass at least 84 nucleotide substitutions (21*4 for genomic DNA) and at least 1680 amino acid substitution! The specification discloses only one polynucleotide of SEQ ID NO: 41 that encodes a wild type human Rhesus D antigen. The specification further discloses one or more missense mutations in SEQ ID NO: 41 that contribute to weak D phenotype wherein the missense mutations occurs in nucleotide position 8 is from C to G, position 29 from G to A, position 48 from G to C, position 340 from C to T, position 446 from C to A, position 544 from T to A, position 594 from A to T, position 602 from C to G, in position 658 from T to C, position 667 from T to G, position 809 from T to G, position from 819 from G to A, position 826 from G to C, position 830 from G to A, position 845 from G to A, position 880 from G to C, position 885 from G to T, position 919 from G to A, position 1016 from G to A, position 1154 from G to C, and position 1177 from T to C of SEQ ID NO: 41 or in a combination of said position. Other than the specific missense mutation in SEQ ID NO: 41 mentioned above, the other nucleic acid molecule carrying other missense mutation that encodes the weak D phenotype is not adequately described. The rejection is maintained for reasons above.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1, 3, 4, 5, 9, 12, and 50-51 stand rejected under 35 U.S.C. 102(a) as being anticipated by Legler *et al* (Transfusion 38(5): 434-40, May 1998; PTO 892).

Legler *et al* teach a polynucleotide that encodes a human Rhesus D antigen contributing to or indicative of the weak D phenotype that has at least one missense mutation as compared to the wild type Rhesus D antigen such as a point mutation at nucleotide 667 (T to G) that resulted in a Phe at amino acid position 223 to Val, Glu at position 233 to Gln and Val at 238 to Met) (See abstract, Figure 3, page 437, column 1, in particular). The reference missense mutations such as positions 223 and 238 are located in the intramembrane region of the reference RhD antigen. Legler et al further teach the reference polynucleotide carries a missense mutation at nucleotide 667 from T to G (See Figure 2, in particular). The reference polynucleotide is genomic DNA (See legend of Figure 2, Materials and methods, in particular). The reference further teaches various oligonucleotides that hybridize to a portion of the reference nucleic acid molecule comprising the reference missense mutation (See Table 1, page 435, in particular). The reference oligonucleotides are 17 nucleotides in length which are within the claimed 12 to 50 or 15 to 24 nucleotides in length. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 5/21/04 have been fully considered but are not found persuasive.

Applicants' position is that the Legler et al reference was published in May 1998, after the January 23, 1998 priority date, Legler et al is not available as prior art against the claims of the subject application.

In contrast to applicant's assertion that that priority date of instant is January 23, 1998, the priority date of instant application is December 18, 1998, which is after the publication date May 1998 of the Legler reference. Therefore, the Legler et al reference is not available as prior art against the claims of the subject application.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1, 2, and 10-12 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Legler *et al* (Transfusion 38(5): 434-40, May 1998; PTO 892) in view of Sambrook *et al* (of record, *Molecular Cloning*, 1989, Cold Spring Harbor Laboratory, CSH, NY, Ch. 17).

The teachings of Legler *et al* have been discussed supra.

The claimed invention in claim 10 differs from the teachings of the reference only that a vector comprising the nucleic acid encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype in its transmembrane and/or intracellular regions as compared to the wild type Rhesus D antigen as set forth in SEQ ID NO: 41 or the nucleic acid molecule carrying at least one missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in amino acid position 114-149 with the proviso that said D antigen does carry not a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or of threonine in position 283 by isoleucine or carrying a gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene.

Sambrook *et al* teach cloning a cDNA into an expression vector, a process of transforming the expression vector into host cells, culturing the host cells under conditions in which the polypeptide is expressed and then recovering the polypeptide from the culture. Sambrook *et al* teach that it is desirable to use recombinant DNA techniques for the production of biologically active proteins in order to produce proteins of higher concentration and purity.

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce any Rhesus D antigen contributing to weak D phenotype by culturing host cell transformed with the vector comprising the polynucleotide taught by Legler *et* and isolating the Rhesus D antigen as taught by Sambrook *et al and* Legler *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because there would be a higher yield of polypeptide with greater purity as taught by Sambrook *et al.*

15. Claims 6, 8 and 49 stand objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

16. No claim is allowed.

17. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

19. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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